Original Research Proposal:

Palladium-Catalyzed Enantioselective 1,4-Conjugate Trifluoromethylation of Michael Acceptors to Form New Tertiary and Quaternary Centers

[redacted]

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Dissertation Committee:

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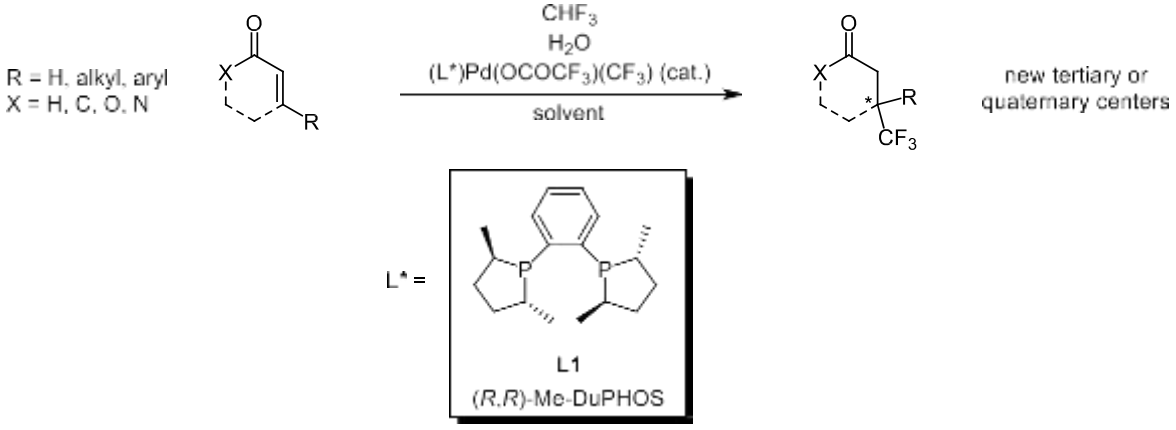
Abstract

A method for the first palladium-catalyzed enantioselective 1,4-conjugate trifluoromethylation of Michael acceptors is proposed herein. The reaction makes use of fluoroform as the source of the trifluoromethyl (CF_3) group and palladium(II) as the sole oxidation state of the metal throughout the course of the reaction. Using the bidentate phosphine ligand (*R*,*R*)-Me-DuPHOS, the stereochemistry of the newly formed chiral center could be controlled to access enantioenriched tertiary and quaternary β-trifluoromethylated carbonyl products. Including water in the reaction would ensure that the palladium(II) enolate intermediate is protonated to release the target Michael addition product and a palladium(II) hydroxide intermediate, thus avoiding the β-hydride elimination pathway that would lead to unwanted Heck products. The proposed method would allow facile access to current and novel chiral trifluoromethylated pharmaceuticals and agrochemicals using fluoroform—a gas that is routinely incinerated on an industrial scale—as the source of the CF_3 group. The method would be efficient and more atom economical than the current known methods for preparing β-trifluoromethylated carbonyl compounds. The importance of this new method is demonstrated with its application toward the formal synthesis of BAY 73-6691, a drug that has shown promising results against Alzheimer's disease.

Specific Aims

There continues to be a vacancy in the chemical literature in regards to the enantioselective 1,4-conjugate addition of a trifluoromethyl group to α,β-unsaturated carbonyls. This is surprising because enantioselective conjugate addition reactions are one of the fundamental methods for forming new carbon-carbon bonds to access β-chiral carbonyl compounds.[1] Since fluorinated pharmaceuticals tend to have enhanced medicinal properties compared to their non-fluorinated forms[2], it is surprising that a method which combines both areas with stereochemical control using a catalytic method is yet to be developed. The goal of this proposal is to outline a method that combines both of these areas of chemistry to arrive at enantioenriched β-trifluoromethylated carbonyl compounds (Scheme 1).

Scheme 1. Asymmetric Pd-catalyzed 1,4-trifluoromethylation of α,β-unsaturated carbonyls



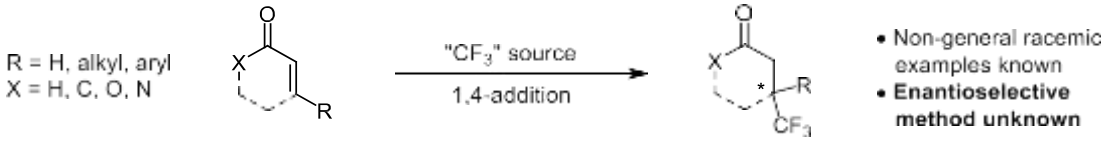
The specific aims of this proposal are as follows:

1) To develop the first method for the palladium(II)-catalyzed asymmetric conjugate addition of a trifluoromethyl group to α,β-unsaturated carbonyl systems to form new enantioenriched tertiary and quaternary centers.
2) To examine the stereoselectivity and scope of the proposed method.
3) To demonstrate the application of the method toward the synthesis of pharmaceuticals.

Background and Significance

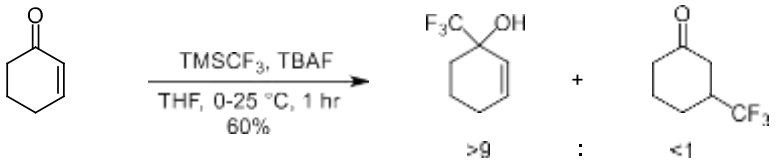
The effort to attain novel fluorinated organic compounds continues to be an active area of research in academia and the pharmaceutical and agrochemical industries. This continued effort is due to the enhanced lipophilicity and bioavailability that ensues following the replacement of hydrogen atoms with fluorine.[2] In regards to the incorporation of a trifluoromethyl group to acyclic α,β-unsaturated aldehydes and ketones, a handful of enantioselective 1,2-trifluoromethylations have been reported—typically with the use of cinchona alkaloids—affording low to moderate enantioselectivities.[2a,c,d,] Although various groups continue their efforts in the search for a more general enantioselective 1,2-trifluoromethylation method that could apply to a broader range of carbonyl substrates, there is already noted progress in this area.[2] However, the enantioselective 1,4-trifluoromethylation of unsaturated carbonyls is still unreported in the chemical literature (Scheme 2).[3]

Scheme 2. Enantioselective 1,4-trifluoromethylation of unsaturated carbonyl systems



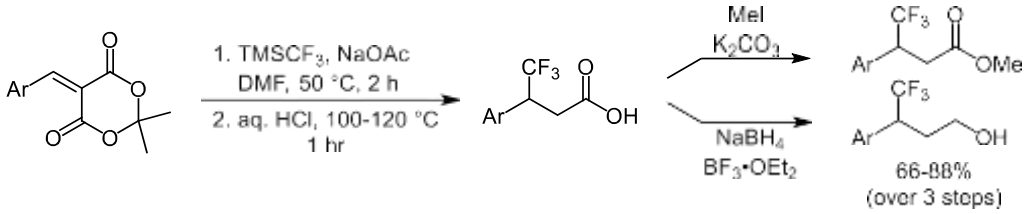
Conjugate 1,4-trifluoromethylation of unsaturated carbonyl systems still languishes well behind the respective 1,2-addition, mainly due to the mismatch between the "hard" nature of the trifluoromethyl anion and the "soft" nature of the alkene.[2b] A handful of reports have demonstrated the 1,4-conjugate trifluoromethylation of Michael acceptors, albeit in poor to moderate yields and only in racemic fashion.[3] The first report of 1,4-trifluoromethylation was reported by Prakash and Olah in 1989 when they treated 2-cyclohexenone with trifluoromethyltrimethylsilane ($TMSCF_3$), affording the conjugate addition product as the minor product (Scheme 3).[4]

Scheme 3. First example of 1,4-trifluoromethylation



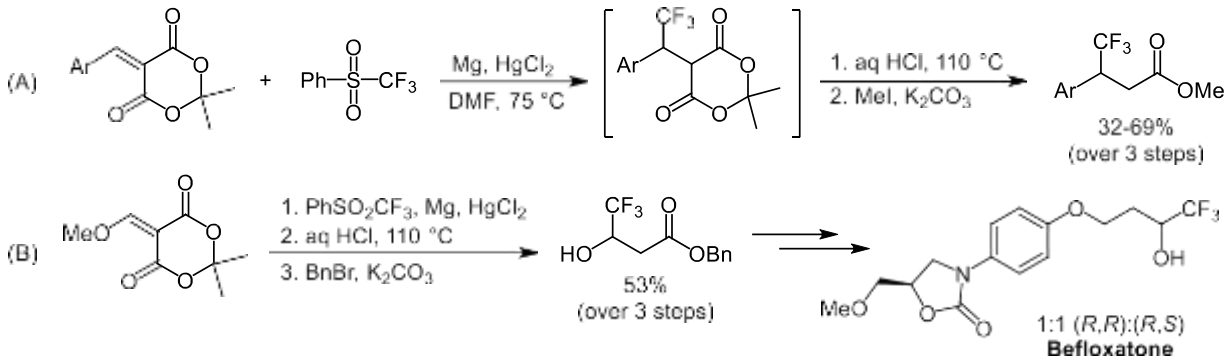
One of the more recent examples of 1,4-trifluoromethylation was demonstrated in 2009 by Dilman and coworkers when they accessed β-trifluoromethylated arylidene Meldrum's acids in moderate yields using $TMSCF_3$ as the trifluoromethyl source (Scheme 4).[5] In order to probe the utility of these building blocks, the trifluoromethylated Meldrum's acids were decarboxylated and either alkylated to afford β-trifluoromethylated methyl esters or reduced to afford trifluoromethyl alcohols—both in moderate to good yields.

Scheme 4. Conjugate trifluoromethylation of Meldrum's acids using $TMSCF_3$



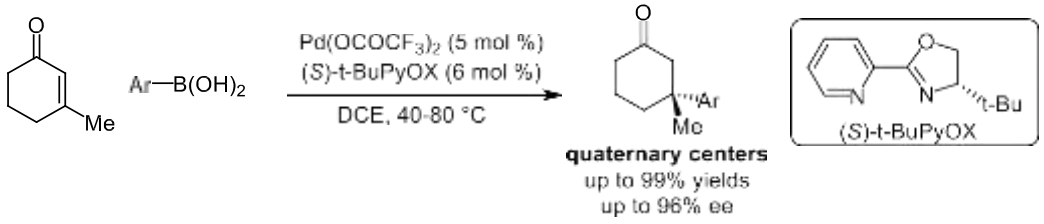
Similarly in 2013, Petersen and coworkers showed that various arylidene Meldrum's acids also proceeded through 1,4-addition when using phenyl trifluoromethyl sulfone and magnesium metal (Scheme 5).[6] Decarboxylation and alkylation was also carried out in this case to afford the corresponding β-trifluoromethylated methyl esters in low to moderate yields (Scheme 5A). Although both methods by Dilman and Peterson successfully add a CF_3 group to the β position of the unsaturated carbonyl system, neither report shows and example of an enantioselective version. In fact, Peterson applied her method toward the synthesis of the reversible and selective monoamine oxidase A (MAO-A) inhibitor Befloxatone (*R,R*), obtaining the target as a 1:1 mixture of diastereomers (Scheme 5B).[6]

Scheme 5. 1,4-Trifluoromethylation of Meldrum's acids using phenyl trifluoromethyl sulfone



The aforementioned examples demonstrate that 1,4-addition of CF_3 is possible; however, the current gap in this area is the lack of an enantioselective method that accomplishes the same goal. In thinking about a method to obtain enantioenriched β-trifluoromethylated products for this proposal, the idea of using palladium with a chiral ligand arose after coming across a 2011 publication by the Stoltz group where they reported the first palladium-catalyzed asymmetric conjugate addition of arylboronic acids to β-substituted cyclic enones (Scheme 6).[7] The method used a chiral pyridinooxazoline ligand and afforded new quaternary centers in high yields and enantioselectivities. After investigating the reaction in more detail, the catalytic cycle was proposed two years later in 2013.[8]

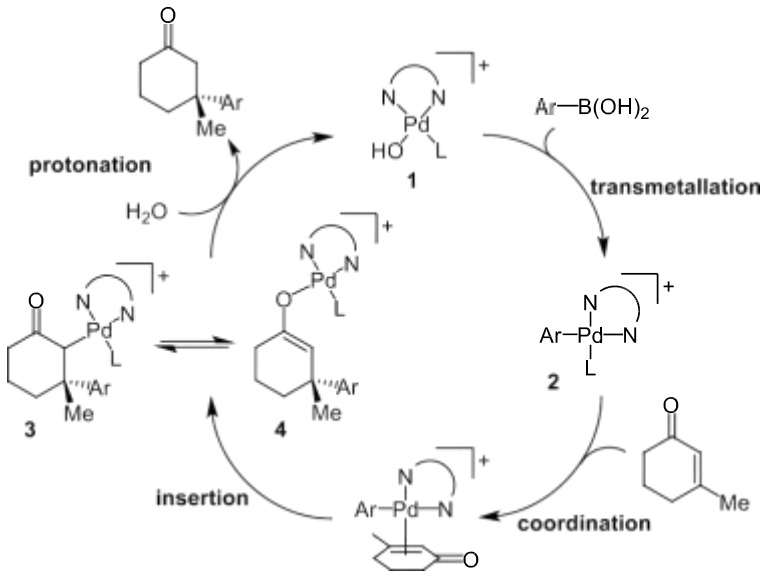
Scheme 6. Asymmetric 1,4-addition of arylboronic acids to cyclic enones (Stoltz)



The mechanism proposed by Stoltz begins with a transmetallation reaction between complex **1** and the arylboronic acid to afford complex **2** (Scheme 7). Coordination of complex **2** with the enone followed by insertion affords **3** and **4** in equilibrium which, after protonation, affords the product and regenerates the active catalyst **1**. It was reasoned that if the hydroxide

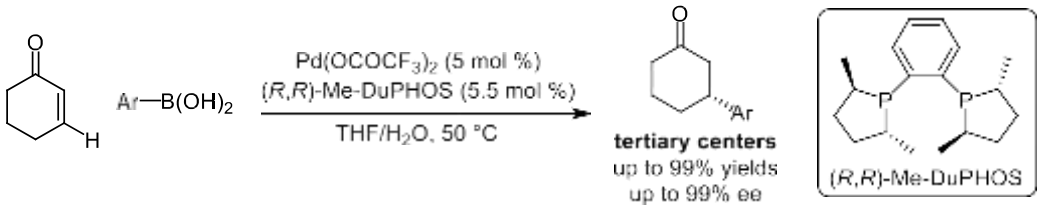
group on complex **1** could be substituted with a CF_3 group to form a trifluoromethylated version of complex **2** (CF_3 instead of aryl), it may also be possible to analogously insert the CF_3 group to the β position of cyclic ketones. Protonation would afford β-trifluoromethyl ketones bearing new quaternary centers and regenerate the active catalyst **1**.

Scheme 7. Proposed mechanism for 1,4-addition of arylboronic acids to cyclic enones (Stoltz)

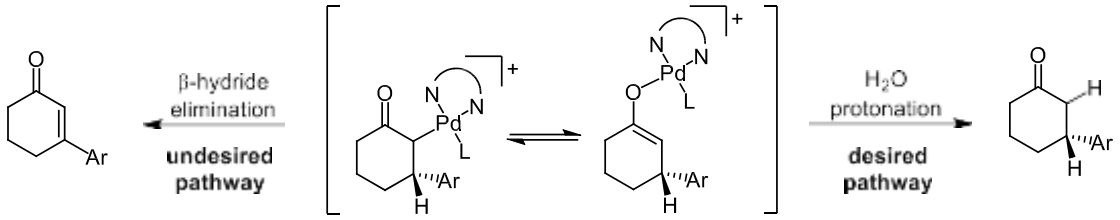


In the work published by Stoltz, all of the cyclic enones used were disubstituted at the β position which lead to quaternary centers in the products. However, Minnaard and coworkers had previously accomplished a similar transformation using enones that were monosubstituted at the β position, leading to new enantioenriched tertiary centers (Scheme 8).[9] In their report, they discuss how cationic palladium enolates are much more susceptible to hydrolytic cleavage than unfunctionalized alkylpalladium species, thereby avoiding the undesired β-hydride elimination pathway (Scheme 9). This is consistent with earlier work carried out by Espinet, Suzuki, and Yamamoto who studied palladium(II) enolates and made similar observations.[10] This work gives rise to the possibility of also generating enantioenriched tertiary centers via 1,4-CF_3 addition when using α,β-unsaturated carbonyl substrates that are monosubstituted at the β position.

Scheme 8. Asymmetric 1,4-addition of arylboronic acids to cyclic enones (Minnaard)



Scheme 9. Palladium(II) enolates favor the protonation pathway in the presence of water



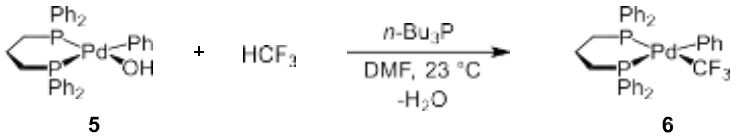
It is worth noting that there are alternative methods to arrive at enantioenriched β-trifluoromethylated carbonyl systems. These methods typically involve having the CF_3 group already pre-installed at the β position of an α,β-unsaturated carbonyl substrate and subjecting it to a Michael-type reaction in the presence of a chiral ligand.[11] Although this approach is generally successful, the β-trifluoromethyl α,β-unsaturated carbonyl substrates are not usually commercially available and, therefore, have to be synthesized. Preparation of these substrates usually involve Wittig and/or Horner-Wadsworth-Emmons olefinations[11b,d-f] or rely on trifluoromethylating reagents like the Togni reagent[11c]—all of which produce stoichiometric waste before the key reaction is even attempted. The method proposed herein, if successful, would enantioselectively add a CF_3 group to a variety of inexpensive and commercially available α,β-unsaturated carbonyl compounds under catalytic conditions using fluoroform—the byproduct of the production of Teflon which is usually incinerated[12]—as the source of the trifluoromethyl group. The overall process would be more efficient, atom economical[13], and possibly more amenable to late-stage synthetic incorporation for the production of new tertiary and quaternary trifluoromethylated centers.

Experimental Design and Methods

1. Development of the title transformation

The method proposed herein began with an evaluation of the catalytic cycle proposed by Stoltz in his 2013 publication[8] to determine if certain steps could be manipulated in order to carry out an analogous conjugate addition with a CF_3 group. Since one of the aims of the proposed method is to be more efficient and atom economical, formation of a Pd-CF_3 complex analogous to **2** (Scheme 7) without the need for super-stoichiometric boron reagents would be desired. Fortunately, work published in 2013 by Grushin and coworkers might be useful for accomplishing this goal. Grushin showed that palladium hydroxide complex **5** could be transformed to Pd-CF_3 complex **6** in nearly quantitative yield under facile conditions using fluoroform and *n*-tributylphosphine (*n*-Bu_3P) as an activator (Scheme 10).[14] This is described as a "push-pull" type of process by the authors in which *n*-Bu_3P coordinates to the metal and pushes electron density to the oxygen which is, simultaneously, being pulled by H-CF_3 via a hydrogen-bonding interaction. This facilitates the release of water, coordination of the CF_3 group to the metal, and release of the *n*-Bu_3P.

Scheme 10. Formation of CF_3-Pd complex **6** using fluoroform as reported by Grushin

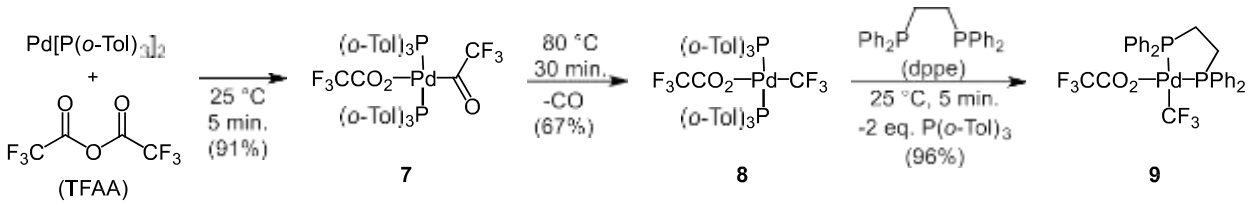


5 **6**

This method for the facile generation of a Pd-CF_3 complex using fluoroform is important for this proposal. However, the ligand used by Grushin to carry out this transformation was 1,3-bis(diphenylphosphino)propane (dppp), a bidentate phosphine ligand. Dppp, which coordinates to the palladium center with two phosphorus atoms (Scheme 10), differs from the pyridine oxazoline ligand employed by Stoltz which binds to the palladium center with two nitrogen

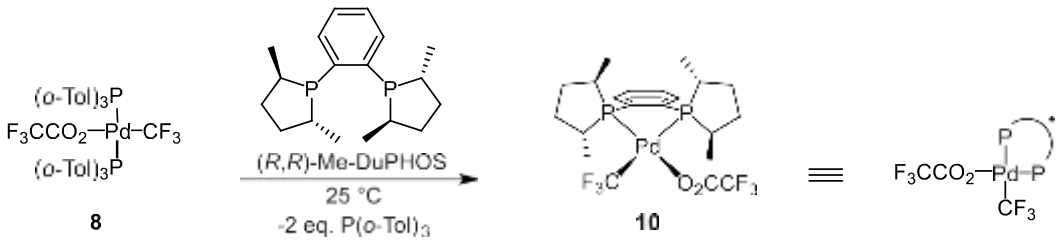
atoms (Scheme 6). Nevertheless, since Minnaard demonstrated that the bidentate phosphine ligand (*R*,*R*)-Me-DuPHOS was effective for his reported enantioselective palladium-catalyzed conjugate addition reactions (Scheme 8), there is precedent that suggests using (*R*,*R*)-Me-DuPHOS would be compatible with the proposed transformation. Using this ligand, it may be possible to form a Pd-CF_3 complex using fluoroform (Scheme 10) that could then, subsequently, insert the CF_3 group to the β position of an unsaturated carbonyl compound.

Scheme 11. Synthesis of Pd-CF_3 complexes **8** and **9** by the Sanford group



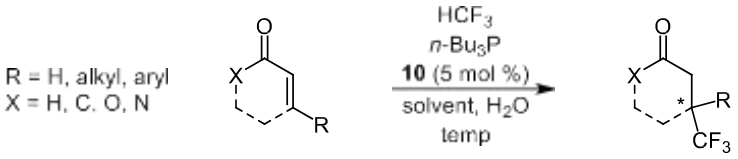
After deciding to incorporate (*R*,*R*)-Me-DuPHOS with Grushin's method for the formation of the Pd-CF_3 intermediate, it was realized that there was another potential problem that needed to be addressed. The Pd-CF_3 complex **6**, if used as is, could possibly insert the phenyl group to the β position of the α,β-unsaturated carbonyl instead of the trifluoromethyl group. In order to avoid this potential problem, a $L_2Pd(X)CF_3$ complex that has a weakly coordinating anion, such as trifluoroacetate ($X = F_3CCO_2^-$), would be preferred in order to eliminate the likelihood of a competing insertion group. Fortunately, the Sanford group synthesized a complex in 2014 that fits this description starting from trifluoroacetic anhydride (TFAA) and a palladium source to form complex **9** (Scheme 11).[15] According to the procedures, complexes **8** and **9** seem bench stable and easy to handle. However, instead of stirring complex **8** with dppe as in the Sanford report, stirring with the chiral phosphine ligand used in this proposal—(*R*,*R*)-Me-DuPHOS—would form Pd-CF_3 complex **10** which is needed for the title reaction being proposed here (Scheme 12).

Scheme 12. Proposed synthesis of key Pd-CF_3 complex **10** from **8** and (*R*,*R*)-Me-DuPHOS



With the preparation of complex **10** (Scheme 12), it would be possible to propose a general reaction scheme for the title reaction. Addition of cyclic or acyclic α,β-unsaturated carbonyl substrates to 5 mol % of complex **10** with fluoroform bubbling into the reaction mixture would form new β-trifluoromethylated carbonyl compounds in high yields and enantioselectivities (Scheme 13). A catalytic amount of *n*-Bu_3P would help facilitate the regeneration of complex **10**, using up to an equivalent if needed as in the Grushin report (Scheme 10). According to the work by Stoltz[8], up to five equivalents of water were added to the reaction mixture whereas, in the work reported by Minnaard[9], up to 55 equivalents of water were added. For the proposed reaction here, a good starting point would be to begin with the addition of 5 equivalents of water. In regards to the temperature, Minnaard conducted his reactions at 50 °C while Stoltz used temperatures ranging from 40-60 °C. Taking these ranges into account, a good starting point may be the middle point at 50 °C.

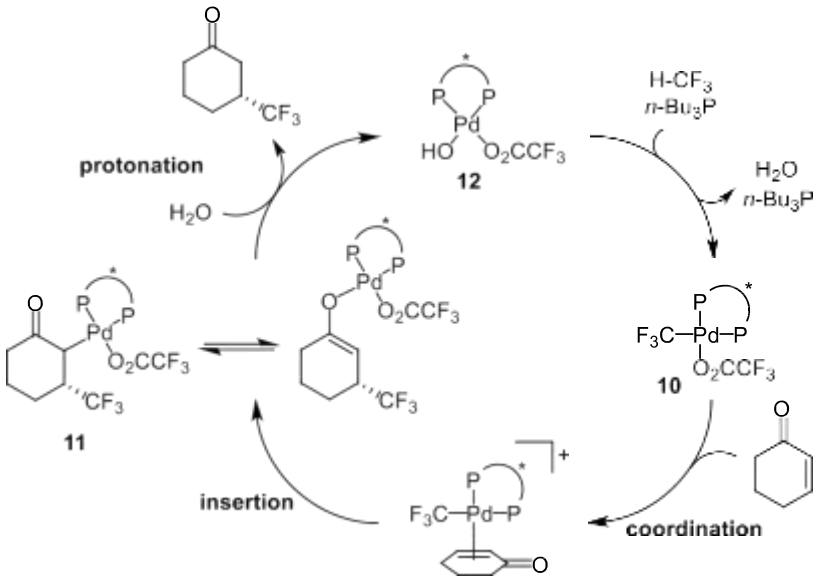
Scheme 13. General reaction for the title transformation



A potential limitation arises when considering the choice of solvent for the reaction. The Pd-CF_3 complex **6** generated by Grushin using fluoroform gave the best result when using DMF as the solvent (Scheme 10). As the polarity of the solvents explored decreased, so did the yield of

complex **6** (8% in THF).[14] Conversely, the work by Minnaard and Stoltz on the conjugate addition of arylboronic acids to α,β-unsaturated carbonyls both used nonpolar solvents, namely THF and 1,2-dichloroethane (DCE), respectively. Stoltz even showed that under his reported conditions, DMF as a solvent provided no product.[16] Taking this information into account, initial test reactions would be conducted using 1,2-dichloroethane. If results are poor using DCE alone, a mixture of DCE with a minimal amount of DMF could also be examined.

Scheme 14. Proposed mechanism for the title transformation

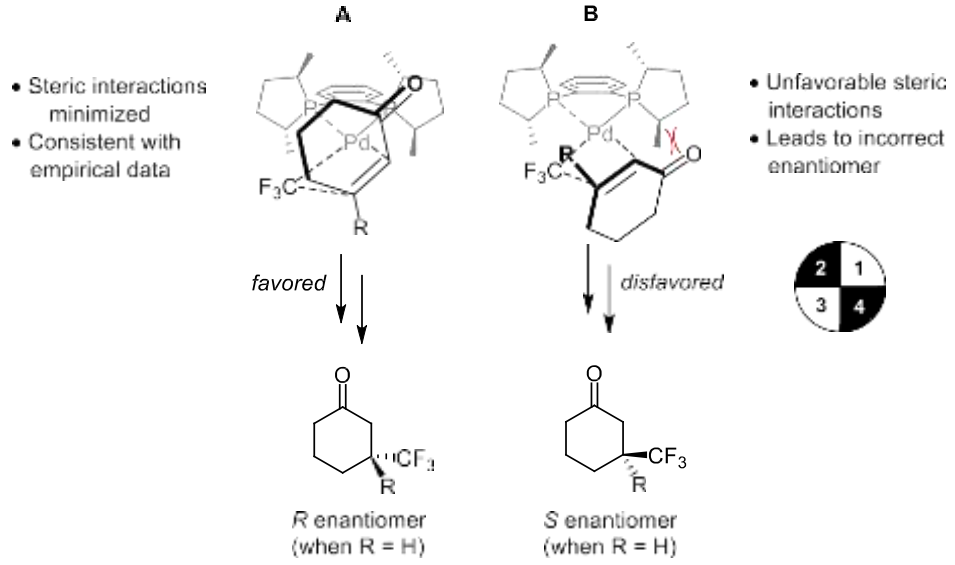


Now that the reaction conditions have been revealed, the proposed reaction mechanism for the title transformation using cyclohexenone as the electrophile can be proposed (Scheme 14). Based on the mechanism published by Stoltz[8], palladium complex **10** would begin the catalytic cycle by coordinating to the π-bond of the unsaturated carbonyl system. Insertion of the trifluoromethyl group at the β-position would give intermediate **11** which, after protonation by water, would afford the target β-trifluoromethylated carbonyl product and intermediate **12**. Based on the method reported by Grushin[14], reaction of intermediate **12** with fluoroform and *n*-Bu_3P as an activator is proposed to regenerate palladium complex **10** and a molecule of water,

completing the catalytic cycle. If this reaction can be optimized to a high efficiency, the only byproducts upon completion of the reaction would be catalytic amounts of complex **10** and *n*-Bu_3P.

2. Stereoselectivity and scope

Figure 1. Proposed model for the stereochemical outcome of the products from cyclohexenone

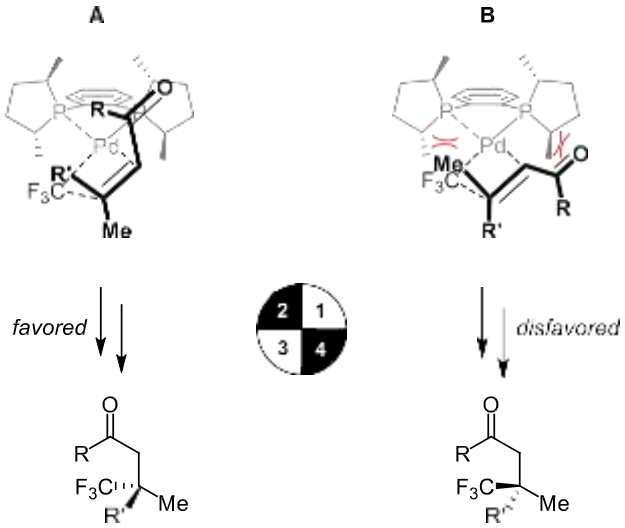


A model that explains the stereoselectivity when using (*R*,*R*)-Me-DuPHOS as the ligand is shown using cyclohexenone (R = H) as the electrophile (Figure 1). Due to the C_2-symmetry of the ligand, there are two possible scenarios for the insertion step. The first scenario is when the *re* face of the alkene approaches the palladium complex (Figure 1A). In this case, the carbonyl oxygen is placed in a position that avoids destabilizing steric interactions with the ligand, depicted as quadrant 1 in the quadrant diagram. Insertion of the CF_3 group would afford the *R* enantiomer in this case. The second scenario is if the alkene were to approach the complex from the *si* face. In this case, the oxygen would be placed in quadrant 4 near the methyl group of the ligand, leading to unfavorable steric interactions (Figure 1B). This particular approach of the

cyclohexenone substrate would give rise to the *S* enantiomer, though the steric interactions would disfavor this pathway from occurring. This model—adopted from the work published by Stoltz[14]—may also explain the *R* enantiomers produced by Minnaard and coworkers when using cyclohexenone along with (*R*,*R*)-Me-DuPHOS and various arylboronic acids (Scheme 8).

In the case where the β position of cyclohexenone is disubstituted (R = alkyl, aryl, etc.), Figure 1A shows how the carbonyl oxygen and the R group would occupy the open quadrants 1 and 3, respectively. On the other hand, approach of the substrate as shown in Figure 1B would be heavily disfavored because the R group and the carbonyl oxygen would be placed in the sterically encumbered quadrants 2 and 4, respectively.

Figure 2. Proposed model for the stereochemical outcome of acyclic α,β-unsaturated carbonyls

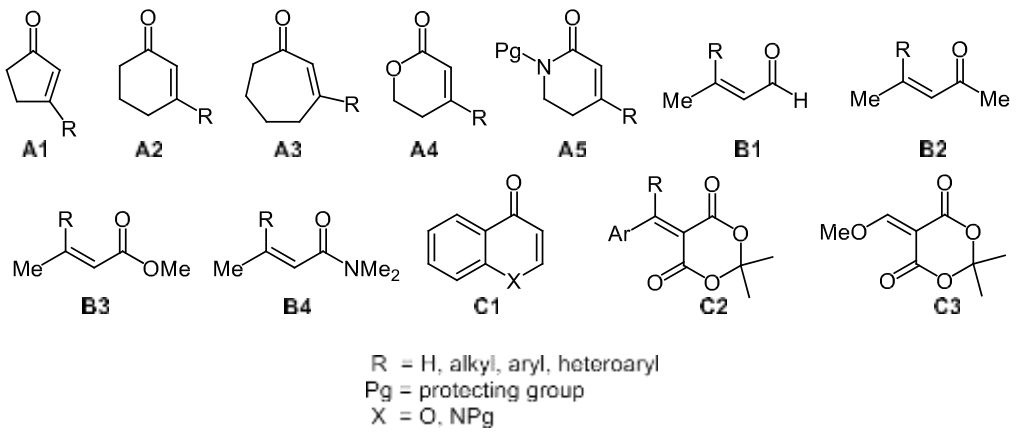


Aside from cyclohexenone, the stereochemistry of acyclic E and Z α,β-unsaturated carbonyl compounds could also be predicted with the proposed model (Figure 2). In the case where the substrates have a trans alkene with monosubstitution at the β position (R'= H), the oxygen and substituent at the β position of the alkene—in these examples, a methyl group—would favor being placed in the open quadrants 1 and 3, respectively, leading to a new tertiary

center (Figure 2A). Alternatively, approach of the substrate as shown in Figure 2B would be unlikely because of unfavorable steric interactions.

In the case of disubstituted alkenes that would give rise to new quaternary centers (R'= alkyl, aryl, etc.), interaction with the ligand is inevitable. Interaction with the ligand can be minimized, however, if R' is restricted to a methyl group. In more extreme cases, alkenes that possess large R' groups would be placed in the sterically encumbered quadrant 2, causing unfavorable steric interactions (Figure 2A). The hypothesis is that this method would work best with trans alkenes.

Table 1. Substrate scope



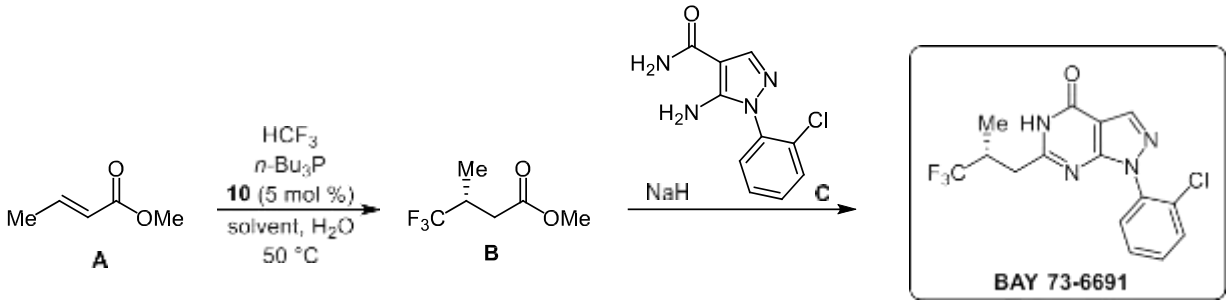
In regards to the scope of the reaction, a good starting point would be to use substrates that performed well in the Minnaard and Stoltz reports. These substrates include cyclic ketones **A1**-**A3** and lactone **A4** (Table 1). Lactam **A5** has not been investigated by either group; however, if used as a substrate, the nitrogen would most likely need to be protected to help prevent coordination to the palladium center. Acyclic aldehydes, ketones, esters, and amides can also be investigated (**B1**-**B4**). Minnaard investigated similar acyclic systems which tended to give lower yields and enantioselectivities.[9] Stoltz also found success with heterocyclic systems analogous to **C1**, so these types of substrates could also be investigated. Lastly, Meldrum's acids could also be

investigated. Specifically, if Meldrum's acid **C3** finds success and gives a good yield with a competitive enantioselectivity, we can apply a formal synthesis of the reversible and selective monoamine oxidase A (MAO-A) inhibitor Befloxatone (*R,R*) with high enantioselectivity (Scheme 4B).

3) *Application of the title method toward the synthesis of pharmaceuticals*

In addition to the aforementioned application of the title method to enantioselectively trifluoromethylate Meldrum's acid **C3** (Table 1) for the formal synthesis of Befloxatone (*R,R*) as a single enantiomer (Scheme 4B), the proposed method could also be applied as the key step in the synthesis of the Alzheimer's drug developed by Bayer, namely BAY 73-6691 (Scheme 13). According to the patent, a racemic version of trifluoromethyl ester **B** is reacted with substrate **C** to afford racemic BAY 73-6691.[17] This means that the last step of Bayer's synthesis of BAY 73-6691, at best, can only afford a 50% yield of the target product. Alternatively, if the method proposed in this document is successful on the acyclic methyl ester **A**, access to enantioenriched methyl ester **B** would be possible and would ultimately result in enantioenriched BAY 73-6691.

Scheme 15. Formal synthesis of BAY 73-6691 using the title transformation as the key step



In conclusion, a method for the first palladium-catalyzed enantioselective 1,4-conjugate trifluoromethylation of Michael acceptors for the formation of new tertiary and quaternary centers has been proposed and investigated. The reaction makes use of fluoroform as the source

of the trifluoromethyl group, (*R*,*R*)-Me-DuPHOS as the chiral ligand, *n*-Bu_3P as an additive, and palladium(II) as the sole oxidation state of the metal throughout the course of the reaction. The reaction would be efficient and atom economical and could be applied toward the synthesis of trifluoromethylated drug compounds such as Befloxatone and BAY 73-6691.

References

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